Certification of Translation

I, Helmut van Heesch of UEXKÜLL & STOLBERG, Patent Attorneys in Hamburg, Germany, do hereby certify that I am conversant with the English and German languages and am a competent translator thereof, and I further certify that to the best of my knowledge and belief the foregoing is a true and correct translation made by me of the document in the English language attached hereto, namely new Claims 1-18 of international Patent Application PCT/-EP97/06893.

Hamburg, June 2, 1999

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Patent claims

(amended claims)

1. Formulation in the form of a matrix material-containing compound with an excipient phase with at least one excipient and/or an active substance phase with at least one active substance, characterized in that the matrix material is chosen from polymers, wherein in case of cellulose materials these cellulose materials are cellulose derivatives, and lipids, the polymer phase and/or the lipid phase of the formulation is incoherent and the excipient and/or active substance phase of the formulation is coherent.

2. Formulation in the form of a matrix material-containing compound with an excipient phase with at least one excipient and/or an active substance phase with at least one active substance, characterized in that the matrix material is chosen from polymers, wherein in case of cellulose the portion of the marix material phase of the formulation is 70 to 98%, and lipids, the polymer phase and/or the lipid phase of the formulation is incoherent and the excipient and/or active substance phase of the formulation is coherent.

3. Formulation according to claim 1 ~~or 2, characterized in that~~ wherein the matrix material phase of the formulation comprises excipient and/or active substance or is free therefrom.

4. Formulation according to one of claims 1 ~~to 3, characterized in that~~ wherein the content of the matrix material phase of the formulation is 1 to 98 %.

5. Formulation according to one of claims 1 ~~to 4, characterized in that~~ wherein the content of the matrix material phase of the formulation is 10 to 95 %.

6. Formulation according to one of claims 1 ~~to 5, characterized~~ wherein ~~in that~~ the content of the matrix material phase of the formulation is more than 15 % and not more than 90 %.

7. Formulation according to one of claims 1 ~~to 6, characterized~~ wherein ~~in that~~ the content of the matrix material phase of the formulation is 40 to 70 %.

8. Formulation according to one of claims 1 ~~to 7, characterized~~ wherein ~~in that~~ the polymeric phase comprises a polyacrylate and/or a polymethacrylate and/or the lipid phase comprises naturally occurring, semi-synthetic and synthetic triglycerides or mixtures thereof, mono- and diglycerides by themselves or in a mixture with one another or with triglycerides, naturally occurring and synthetic waxes, fatty alcohols, including their esters and ethers, and lipid peptides, in particular synthetic mono-, di- and triglycerides as individual substances or in a mixture, specifically hydrogenated fat, glycerol tri-fatty acid esters, specifically glycerol trilaurate, -myristate, -palmitate, -stearate and -behenate, and waxes, specifically cetyl palmitate and cera alba (bleached wax, German Pharmacopeia, 9th edition) or beeswax.

9. Formulation according to one of claims 1 ~~to 8, characterized~~ wherein ~~in that~~ the polymer phase comprises a polyacrylate and/or a polymethacrylate, a cellulose derivative or naturally occurring polymer and/or the lipid phase comprises a naturally occurring lipid.

10. Formulation according to one of claims 1 ~~to 9, characterized~~ wherein ~~in that~~ it comprises at lease one active substance.

11. Formulation according to one of claims 1 ~~to 10, characterized in that~~ wherein the excipient phase comprises at least one filler, in particular chosen from monosaccharides, disaccharides, polysaccharides, sugar alcohols and calcium phosphate, and/or at least one binder, in particular chosen from polyvinylpyrrolidone, gelatine, starch paste, celluloses, cellulose ethers and sugars.

12. Formulation according to ~~one of the preceding claims, characterized in that~~ claim 1 wherein it is in the form of a compressed unit which can be prepared by direct compression.

13. Process for the preparation of a formulation in the form of a matrix material-containing compound according ~~to one of claims 1 to 12, characterized in that~~ to claim 1 wherein the phases of the formulation are suspended or suspended and dissolved together in a liquid, the matrix material phase being insoluble in the liquid, and this suspension is then spray dried.

14. Process for the preparation of a formulation in the form of a matrix material-containing compound according ~~to one of claims 1 to 12, characterized in that~~ claim 1 wherein the phases of the formulation are suspended or suspended and dissolved together in a liquid, the matrix material phase being insoluble in the liquid, and this suspension is then dried in a moving bed or fluidized bed drier.

15. Process according to claim 13 ~~or 14, characterized in that~~ wherein the liquid is an aqueous or organic suspending agent.

16. Process according to one of claims 13 to ~~15, characterized in that~~ wherein at least one binder and/or at least one wetting agent and/or at least one plasticizer is added to the suspension.

17. Use of the formulation in the form of a matrix material-containing compound according to ~~one of claims 1 to 12~~ claim 1 for the preparation of larger matrix units with controlled release properties by known processes.

18. Use of the formulation in the form of a matrix material-containing compound according to ~~one of claims 1 to 12~~ claim 1 for the preparation of tablets and/or larger matrix units with controlled release properties by means of direct compression.

Formulation in the form of a matrix material-excipient compound, matrix material-active substance compound and/or matrix material-excipient-active substance compound, and processes for the preparation thereof and the use thereof for the preparation of tablets and/or other larger matrix units

The invention relates to a formulation in the form of a compound which has an excipient phase with at least one excipient and/or an active substance phase with at least one active substance and a phase of a matrix-forming material (also called matrix material in the following) chosen from polymer and/or lipid, i.e. a polymeric phase and/or a lipid phase with at least one polymer or lipid, and therefore to polymer- and/or lipid-containing delayed/prolonged release dosage forms, processes for the preparation thereof and the use thereof, in particular for the preparation of tablets or other larger matrix units.

Such compounds are physical combinations of at least two starting substances and are employed in particular in the pharmaceuticals sector.

To achieve a release of active substances from a formulation which is controlled, delayed, prolonged or independent of physiological parameters, it is known to process the starting substances such that the resulting formulations or the medicament forms prepared from these formulations have a coating which controls the release (e.g. of polymers, such as polymethacrylates, or organic molecules, such as shellac or cellulose acetate phthalate) or alternatively have a matrix system comprising polymers.

Matrix units for controlled release which are prepared using polymers are described in the literature:

1. polymer particles
   (e.g. pellets, granule grains, microparticles)
2. larger matrix units
   (e.g. tablets, coated tablet cores and implants).

The particles described in more detail in the following are characterized in that the active substance is embedded in the polymeric phase in a molecularly disperse or particulate form.

The larger matrix units described in more detail in the following must as a rule be prepared by the expensive process of compression after prior granulation.

Medicament forms/drug formulations for controlled release using polymers:

The release-controlling effect of such a formulation or medicament form, also called "controlled release" formulation (CR formulation), is controlled on the one hand by the properties of the polymeric phase itself, such as, for example, the wettability, the swellability or the crystallinity, and on the other hand by the structure of the matrix formed by the polymeric phase. This matrix structure, which can be homogeneous or heterogeneous in construction, either is already present in the formulation itself or forms during processing during formulation to the medicament form.

The solubility properties may be mentioned here as properties of the polymeric phase which influence the release. Thus, because of their insolubility and/or swellability in aqueous solvents, polymers ormacromolecules are suitable for delayed release of active substances which are embedded in a matrix of such polymers or macromolecules. Medicament forms with polymer substances which, because of the solubility of the polymers in gastric or intestinal juice, are a formulation which controls the site of the release are furthermore known.

A distinction may be made in particular between two groups in particular of these formulations which control the

release of active substances.

On the one hand, polymer-containing particles of an order of size of approx. 0.01 to 2 mm, which are also called microparticles (0.05 to 0.2 mm), granule grains or pellets, are known. However, the microparticles or microspherules having a typical size of 50 to 200 µm, nanoparticles, nanopellets and nanospherules which have only been known for a relatively short time are also assigned to the group of polymer-containing particles if they have a polymeric phase. The particles are present as an independent release unit (single dosage unit) in the form of a particulate matrix, the formulation then already having a matrix structure.

On the other hand, the particles described in the present application can be combined to larger release units or larger matrix units. This further processing is described in detail below.

Examples which may be mentioned of particulate matrices, the particles of which form independent release units, are the dispersion of microparticles for parenteral injection, which allow a controlled release of LH-RH analogues, and the filling of pellets into a gelatine capsule in the case of commercial preparations, such as sympathomimetics. These are described by Müller, R.H., Hildebrand G.E. (eds.) in "Pharmazeutische Technologie: Moderne Arzneiformen [Pharmaceutical Technology: Modern Drug Dosage Forms]", Wissenschaftliche Verlagsgesellschaft mbH Stuttgart, (1997), by Bauer, K.H., Frömming, K-H., Führer, C. in "Pharmazeutische Technologie [Pharmaceutical Technology]" Georg Thieme Verlag Stuttgart, New York, (1991), and by List, P.H. "Arzneiformenlehre [Pharmaceutical Dosage Forms]" Wissenschaftliche Verlagsgesellschaft mbH Stuttgart, (1986).

EP 0 261 677 furthermore describes polymer-containing compositions which are said to allow a delayed release of the active substance. A spray drying process is disclosed for the preparation of these compositions, so that by applying the doctrine of this publication, particles having a size of at least 30 µm which contain the active substance in a uniform distribution are obtained.

Several processes are described in the literature for the preparation of such formulations with a particulate matrix structure.

In the processes by the "solvent evaporation" or "in-liquid drying" method, the polymer or the matrix-forming agent is a substance (e.g. polymers, such as polylactides or polylactide/glycolide) which is soluble in an organic solvent. The polymer is dissolved in an organic solvent and the active substance is also dissolved or - in the case of insoluble active substances - dispersed in the organic phase. The polymer or matrix-forming agent solution comprising the active substance is then added to an aqueous surfactant solution and an O/W emulsion is prepared by stirring. The organic solvent is then removed and the matrix-forming agent precipitates. Solid pellets or microparticles are formed. A distinction is made between the "solvent evaporation" and the "in-liquid drying" method, depending on the method of removal of the solvent.

These processes have been described by Speiser, P. in Müller, R.H., Hildebrand G.E. (eds.) in "Pharmazeutische Technologie: Moderne Arzneiformen [Pharmaceutical Technology: Modern Drug Dosage Forms]", Wissenschaftliche Verlagsgesellschaft mbH Stuttgart, (1997) by Beck, L.R., Pope, V.Z., Cowsar, D.R., Lewis, D.H., Tice, T.R., in "Evaluation of a new three-month injectable contraceptive microsphere system in primates (baboons)", Contracept.

Deliv. 1 Syst., 1, 79-80 (1980), by Beck, L.R., Flowers, C.E., Pope, V.Z., Tice, T.R., Wilborn, W.H., in "Clinical evaluation of an improved injectable microcapsule contraceptive system" in Amer. J. Obstet. Gynecol. 147 (7), 815-821 (1983) and by Beck, L.R., Pope, V.Z., Flowers, C.E., Cowsar, D.R., Tice, T.R., Lewis, D.H., Dunn, R.L., Moore, A.B., Gilley, R.M., in "Poly(d,l-lactidecoglycolide)/norethisterone microcapsules: An injectable biodegradable contraceptive" in Biol. Reprod. 28, 186-195 (1983a).

Very fine particles in the region of a few micrometres can be obtained by these processes. However, the large outlay with which the preparation method is associated and the contamination of the particles with residual solvent are disadvantages. For this reason, there is also as yet no product in Germany which has been prepared by one of these processes and meets the approval criteria for a medicament. Alternatively, the polymer or matrix-forming agent solution comprising the active substance can be spray dried. Here also, a residual content of organic solvents in the products cannot be avoided because of the preparation process. Products prepared by this process, such as e.g. microparticles for parenteral administration of bromocriptine, are described by Fahr, A., Kissel, T., in Müller, R.H., Hildebrand G.E. (eds.) in "Pharmazeutische Technologie: Moderne Arzneiformen [Pharmaceutical Technology: Modern Drug Dosage Forms]", Wissenschaftliche Verlagsgesellschaft mbH Stuttgart, (1997). They are available on the pharmaceuticals market. However, the problem of the residual solvent content has only been shifted in that here also the release of the toxic solvent is delayed and therefore occurs in a small daily amount. The amount released from the matrix per day remains below the maximum daily tolerated value.

All the processes mentioned so far are characterized in

that the polymeric phase or the matrix-forming agent is present as a molecule in a dissolved form and is in an organic solvent. Particulate formulations, the polymeric phase of which comprises the active substance in a molecularly disperse form or in the form of fine particles are formed. These formulations have a so-called homogenous matrix structure, as is also described by Fahr, A., Kissel, T. in Müller R.H., Hildebrand G.E. (eds.) in "Pharmazeutische Technologie: Moderne Arzneiformen [Pharmaceutical Technology: Modern Drug Dosage Forms]", Wissenschaftliche Verlagsgesellschaft mbH Stuttgart, (1997).

Another process for the preparation of a particulate formulation with a polymeric phase avoiding the use of organic solvents is described in EP 0 361 677. The matrix-forming agent, which is water-soluble according to this publication, or the polymeric phase is dissolved in water (e.g. ethyl acrylate/methacrylate copolymer in ammoniacal solution), the active substance is also dissolved or dispersed and - in contrast to the "solvent evaporation" and "in-liquid drying" method - instead of an O/W a W/O emulsion is now prepared. Dispersion media are water-immiscible organic solvents, e.g. liquid paraffin or methylene chloride. The matrix-forming agent can be dissolved in water or also emulsified in the aqueous phase. In the second case, an emulsion in a water-immiscible organic solvent is dispersed. Polymer particles which include the active substance in a molecularly disperse or particulate distribution are precipitated by expensive azeotropic distillation of water and the organic solvent. The particles are obtained by separation by means of filtration and subsequent washing.

US-A-5 043 280 describes a process for the preparation of a particulate formulation by extraction in supercritical gases. In this case, the matrix-forming agent - as in the

"solvent evaporation" - is a substance which is soluble in an organic solvent, such as e.g. a polymer. The polymer is dissolved in an organic solvent and the active substance is also dissolved or - in the case of insoluble active substances - dispersed in the organic phase. The matrix-forming agent solution comprising the active substance is then finely sprayed into a supercritical gas phase. Fine drops are distributed in the supercritical gas, which extracts the organic solvent from the drops. Precipitation of particles which comprise the active substance occurs as a result.

These processes mentioned also lead to formulations which contain the active substance in a molecularly disperse or particulate form embedded in the polymeric phase. As a result of this process-related inclusion of the active substance into the polymeric phase, the external phase of the formulation mostly comprises polymer, which also determines the pharmaceutical properties, which are of importance for any possible further processing. The formulations mentioned furthermore have the disadvantage that they can be prepared only with considerable expenditure of cost and time.

The possibility of further processing of particulate, polymer-containing formulations to medicament forms which have larger matrix units, such as, for example, to tablets, coated tablet cores or implants, is known. The preparation of implants comprising LH-RH analogues is thus described by Müller, R.H., Hildebrand G.E. (eds.) in "Pharmazeutische Technologie: Moderne Arzneiformen [Pharmaceutical Technology: Modern Drug Dosage Forms]", Wissenschaftliche Verlagsgesellschaft mbH Stuttgart, (1997). The preparation of tablets is of particular importance here, because this medicament form has many advantages, such as, for example, the possibility of processing almost all

solid active substances, the high dosage accuracy, the easy taking and handling and the good storability and transportability.

Medicament forms which are larger matrix units, and in particular tablets, are usually prepared by compression. Several process steps are necessary here for processing conventional polymer-containing formulations in the form of particulate matrices.

The various constituents, such as, for example, various active substances, excipients and polymers, are first mixed homogeneously. The mixture is then subjected to wet granulation by addition of binders, granulating fluid or solvents. The resulting granules are dried to remove the residual moisture. Compression to tablets, coated tablet cores or implants is then carried out with the dry granules with the addition of further excipients, such as flow regulators, lubricants and mould release agents.

The fact that the active substance is exposed to the moisture of the granulation fluid or solvent for a long time during the wet granulation and unavoidably is exposed to an elevated temperature during the necessary drying process is a disadvantage. Furthermore, because of the various individual steps and the devices and apparatuses required for these, the process is associated with a relatively high expenditure of time and is therefore cost-intensive.

Direct compression of tablets from formulations with polymeric constituents, which is already often used for the preparation of tablets without a polymeric phase because of the low costs and the rapid implementation, has hitherto not been possible because of the following difficulties.

On the one hand, due to predominantly elastic deformation, the polymers have poor compression properties, since compression is usually achieved chiefly by plastic deformation.

On the other hand, the mixture for direct compression tends towards an undesirable demixing between powdered active substances and/or excipients and polymers because of the different nature of the surfaces and the resulting different flow properties. In direct compression, highly inhomogeneous tablets would therefore be obtained due to the progressive demixing of the tablet-forming material.

The generally poor flow properties of the polymers are another problem. As a result of this, a satisfactory delayed/prolonged release effect is not achieved because of the limited capacity for admixing of polymers to the tablet-forming mixture. In the literature, an addition of as a rule a maximum of 10-15 % polymer in a tablet recipe for direct compression is described for acrylate polymers by McGinity, J.W., Cameron, C.G., Cuff, G.W., in "Controlled-release theophylline tablet formulations containing acrylic resins. I. Dissolution properties of tablets", Drug Development and Industrial Pharmacy, 9 (162), 57-68 (1983) and by Cameron, C.G., McGinity, J.W., in "Controlled-release theophylline tablet formulations containing acrylic resins, II. Combination resin formulations" and "III. Influence of filler excipient", loc. cit. 13 (8), 1409-1427 (1987), loc. cit. 13 (2), 303-318 (1987).

However, delayed/prolonged release dosage forms in which lipids are used are also known. Such dosage forms described in the literature for controlled release using lipids are substantially:

1. suppositories
2. vaginal globuli
3. pellets for peroral administration (e.g. Mucosolvan retard).

In comparison with polymers, lipids offer the following advantages:

1. good tolerability in vivo, especially if they are composed of physiological fatty acids
2. no toxicologically unacceptable residues from the production (e.g. catalyst residues)
3. control of the degradation rate in vivo via the chemical structure of the lipids
4. inexpensive

They are therefore excipients which can be employed in addition to polymers for the preparation of CR formulation.

Medicament/drug dosage forms for controlled release using lipid formulations from compounds:

Suppositories and vaginal globuli are as a rule prepared by pouring out the medicament-containing mixture into moulds (P.H. List, Arzneiformenlehre, [Pharmaceutical Dosage Forms], Wissenschaftliche Verlagsgesellschaft 1976).

It is also possible to prepare suppositories by compression of a mixture of lipid particles and drug powder, but preparation on a large industrial scale presents difficulties because of the generally poor flow properties of these mixtures when filling the compression moulds. This method is therefore primarily described for small-scale preparation on a recipe scale in the pharmacy (K. Münzel, J. Büchi, O.-E, Schultz, Galenisches Praktikum [Practical Galenics], Wissenschaftliche Verlagsgesellschaft Stutt-

gart, p. 652, 1959). Only lipids which melt or at least soften at body temperature are employed here.

Pellets which are prepared on a large industrial scale by extrusion of molten lipids with an extruder and a perforated disc are medicament forms for peroral administration (Voigt, Lehrbuch der Pharmazeutischen Technologie, [Textbook of Pharmaceutical Technology], Verlag Chemie, 1975). Disadvantages here are e.g. the incorporation of the drugs into the lipid (e.g. by dispersion or dissolving), the exposure of the drugs to heat during extrusion and the need for further processing of the pellets in an additional production step (e.g. introduction into hard gelatine capsules).

The object of the present invention is thus to provide a formulation in the form of a matrix material-containing compound, as a retarded action medicament formulation, which has an excipient and/or an active substance (drug) phase and a matrix material phase. The formulation should have a sufficiently high matrix material content so that controlled release of the active substance contained therein or added subsequently during processing to larger matrix units is made possible. Furthermore, it should be possible to process the formulation to larger matrix units by means of direct compression (e.g. tabletting). Moreover, a process for the preparation of this formulation or compound is to be provided.

The object according to the invention is achieved by a matrix material-containing retarded action medicament form which is in the form of a matrix material-excipient compound, matrix material-active substance compound and/or matrix material-excipient-active substance compound, the matrix material being chosen from polymers and lipids such that the compound has a polymeric phase and/or lipid phase

and an excipient and/or an active substance phase. Such a compound can be converted into its final medicament form by direct compression.

The invention therefore relates to polymer- or lipid-containing formulations which

- are in the form of a compound which has a polymeric or lipid phase with at least one polymer or lipid, an excipient phase with at least one excipient and/or an active substance phase with at least one active substance.

According to the invention, it has been recognized that the object can be achieved by the formulation described in claim 1, which

a) has an excipient phase with at least one excipient and/or an active substance phase with at least one active substance and a polymeric phase with at least one polymer, the polymeric phase being incoherent and the excipient and/or active substance phase being coherent, or

b) has a lipid phase with at least one lipid, an excipient phase with at least one excipient and/or an active substance phase with at least one active substance, the lipid phase being incoherent and the excipient and/or active substance phase being coherent.

In particular, the polymer phase or the lipid phase can comprise excipient and/or active substance or be free from these.

In the formulation according to the invention, the content of polymer phase or lipid phase can be between 1 and 98 %,

based on the total amount of excipient and/or active substance phase and polymer phase or lipid phase.

In particular, the formulation can have a content of polymer/lipid phase of 10 to 95 %.

The content of polymer/lipid phase in the formulation can furthermore be more than 15 % and not more than 90 %.

However, for implementing the present invention, it is particularly advantageous if the polymer/lipid phase has a content of 40 to 70 %, based on the total amount of excipient and/or active substance phase and polymer/lipid phase.

In principle, the formulation according to the invention can comprise any type of active substance or be free from active substance. The active substance can furthermore be added to the formulation subsequently, e.g. before a further processing to larger matrix units. In general, the formulation can comprise the following groups of active substances:

- hydroxylated hydrocarbons
- carbonyl compounds, such as ketones (e.g. haloperidol), monosaccharides, disaccharides and amino sugars
- carboxylic acids, such as aliphatic carboxylic acids, esters of aliphatic and aromatic carboxylic acids, esters with basic substituents of aliphatic and aromatic carboxylic acids (e.g. atropine scopolamine), lactones (e.g. erythromycin), amides and imides of aliphatic carboxylic acids, amino acids, aliphatic aminocarboxylic acids, peptides (e.g. ciclosporins), polypeptides, β-lactam derivatives, penicillins, cephalosporins, aromatic carboxy-

lic acids, (e.g. acetylsalicylic acid), amides of aromatic carboxylic acids, vinylogous carboxylic acids and vinylogous carboxylic acids esters

- carboxylic acid derivatives, such as urethanes and thiourethanes, urea and urea derivatives, guanidine derivatives, hydantoins, barbituric acid derivatives and thiobarbituric acid derivatives
- nitro compounds, such as aromatic nitro compounds and heteroaromatic nitro compounds
- amines, such as aliphatic amines, aminoglycosides, phenylalkylamines, ephedrine derivatives, hydroxyphenylethanolamines, adrenaline derivatives, amphetamine derivatives, aromatic amines and derivatives, quaternary ammonium compounds
- sulphur-containing compounds, such as thiols and disulphanes, sulphones, sulphonic acid esters and sulphonic acid amides
- polycarbocyclic compounds, such as tetracyclines, steroids with an aromatic ring A, steroids with an alpha,beta-unsaturated carbonyl function in the ring A and an alpha-ketol group (or methylketo group) on C-17, steroids with a butenolide ring on C-17, steroids with a pentadienolide ring on C-17 and seco-steroids
- O-containing heterocyclic compounds, such as chromane derivatives (e.g. cromoglicic acid)
- N-containing heterocyclic compounds, such as pyrazole derivatives (e.g. propyphenazone, phenylbutazone)
- imidazole derivatives (e.g. histamine, pilocarpine), pyridine derivatives (e.g. pyridoxine, nicotinic acid), pyrimidine derivatives (e.g. trimetoprim), indole derivatives (e.g. indometacin), lysergic acid derivatives (e.g. ergotamine), yohimban derivatives, pyrrolidine derivatives, purine derivatives (e.g. allopurinol), xanthine derivatives, 8-hydroxyquinoline derivatives, amino-hydroxy-alkylated

quinolines, aminoquinolines, isoquinoline derivatives (e.g. morphine, codeine), quinazoline derivatives, benzopyridazine derivatives, pteridine derivatives (e.g. methotrexate), 1,4-benzodiazepine derivatives, tricyclic N-containing heterocyclic compounds, acridine derivatives (e.g. ethacridine) and dibenzazepine derivatives (e.g. trimipramine)

- S-containing heterocyclic compounds, such as thioxanthene derivatives (e.g. chlorprothixene)
- N,O- and N,S-containing heterocyclic compounds, such as monocyclic N,O-containing heterocyclic compounds, monocyclic N,S-containing heterocyclic compounds, thiadiazine derivatives, bicyclic N,S-containing heterocyclic compounds, benzothiadiazine derivatives, tricyclic N,S-containing heterocyclic compounds and phenothiazine derivatives
- O,P,N-containing heterocyclic compounds (e.g. cyclophosphamide)

The following drugs (as the salt, ester or ether or in the free form) are suitable, for example, for incorporation:

Analgesics/antirheumatics

narcotic substances, such as morphine, codeine, piritramide, fentanyl and fentanyl derivatives, levomethadone, tramadol, diclofenac, ibuprofen, indometacin, naproxen, piroxicam, penicillamine

Antiallergics

pheniramine, dimetindene, terfenadine, astemizole, loratidine, doxylamine, meclozine, bamipine, clemastine

Antibiotics/chemotherapeutics

of these: polypeptide antibiotics, such as colistin, polymyxin B, teicplanin, vancomycin; malaria agents,

such as quinine, halofantrine, mefloquine, chloroquine, virustatic agents, such as ganciclovir, foscarnet, zidovudine, aciclovir and others, such as dapsone, fosfomycin, fusafungine, trimetoprim

Antiepileptics

phenytoin, mesuximide, ethosuximide, primidone, phenobarbital, valproic acid, carbamazepine, clonazepam

Antimycotics

a) internal:
nystatin, natamycin, amphotericin B, flucytosin, miconazole, fluconazole, itraconazole

b) external furthermore:
clotrimazole, econazole, tioconazole, fenticonazole,
bifonazole, oxiconazole, ketoconazole, isoconazole, tolnaftate

Corticoids (internal agents)

aldosterone, fludrocortisone, betametasone, dexametasone, triamcinolone, fluocortolon, hydroxycortisone, prednisolone, prednylidene, cloprednol, methylprednisolone

Dermatological agents

a) Antibiotics:
tetracycline, erythromycin, neomycin, gentamycin, clindamycin, framycetin, tyrothricin, chlortetracycline, mipirocin, fusidic acid

b) Virustatic agents as above, and furthermore:
podophyllotoxin, vidarabine, tromantadine

c) Corticoids as above, and furthermore:
amcinonide, fluprednidene, alclometasone, clobetasol, diflorasone, halcinonide, fluocinolone,

clocortolone, flumetasone, diflucortolone, fludroxycortide, halometasone, desoximetasone, fluocinolide, fluocortin butyl, fluprednidene, prednicarbate, desonide

Diagnostics

a) radioactive isotopes, such as Te99m, In111 or I131, covalently bonded to lipids or lipoids or other molecules or in complexes

b) highly substituted iodine-containing compounds, such as e.g. lipids

Haemostyptics/antihaemorrhagics

blood clotting factors VIII, IX

Hypnotics, sedatives

cyclobarbital, pentobarbital, phenobarbital, methaqualone (BTM), benzodiazepines, (flurazepam, midazolam, nitrazepam, lormetazepam, flunitrazepam, triazolam, brotizolam, temazepam, loprazolam)

Hypophysis and hypothalamus hormones, regulatory peptides and their inhibitors

corticotrophin, tetracosactide, chorionic gonadotrophin, urofollitrophin, urogonadotrophin, somatrophin, metergoline, bromocriptine, terlipressin, desmopressin, oxytocin, argipressin, ornipressin, leuprorelin, triptorelin, gonadorelin, buserelin, nafarelin, goselerin, somatostatin

Immunotherapeutics and cytokines

dimepranol 4-acetamidobenzoate, thymopentin, α-interferon, β-interferon, γ-interferon, filgrastim, interleukins, azathioprine, ciclosporin

Local anaesthetics

internal:

butanilicaine, mepivacaine, bupivacaine, etidocaine, lidocaine, articaine, prilocaine

external furthermore:

propipocaine, oxybuprocaine, tetracaine, benzocaine

Migraine agents

proxibarbal, lisuride, methysergide, dihydroergotamine, clonidine, ergotamine, pizotifen

Narcotic agents

methohexital, propofol, etomidate, ketamine, alfentanil, thiopental, droperidol, fentanyl

Parathyroid hormones, calcium metabolism regulators

dihydrotachysterol, calcitonin, clodronic acid, etidronic acid

Ophthalmological agents

atropine, cyclodrine, cyclopentolate, homatropine, tropicamide, scopolamine, pholedrine, edoxudine, idoxuridine, tromantadine, aciclovir, acetazolamide, diclofenamide, carteolol, timolol, metipranolol, betaxolol, pindolol, befunolol, bupranolol, levobununol, carbachol, pilocarpine, clonidine, neostimgine

Psychotropic agents

benzodiazepines (lorazepam, diazepam), clomethiazole

Thyroid therapeutics

l-thyroxine, carbimazole, thiamazole, propylthiouracil

Sera, immunoglobulins, vaccines

a) general and specific immunoglobulins, such as hepatitis types, rubella, cytomegaly, rabies, early summer meningoencephalitis, varicella-zoster, tetanus, rhesus factors

b) immune sera, such as botulism antitoxin, diphtheria, gas gangrene, snake poison, scorpion poison

c) vaccines, such as influenza, tuberculosis, cholera, diphtheria, hepatitis types, early summer meningoencephalitis, rubella, Haemophilus influenzae, measles, Neisseria, mumps, poliomyelitis, tetanus, rabies, typhus

Sex hormones and their inhibitors

anabolics, androgens, antiandrogens, gestagens, oestrogens, antioestrogens (tamoxifen etc.)

Cystostatics and metastases inhibitors

a) alkylating agents, such asnimustine, melphalan, carmustine, lomustine, cyclophosphamide, ifosfamide, trofosfamide, chlorambucil, busulfan, treosulfan, prednimustine, thiotepa

b) antimetabolites, such as cytarabine, fluorouracil, methotrexate, mercaptopurine, tioguanine

c) alkaloids, such as vinblastine, vincristine, vindesine

d) antibiotics, such as aclarubicin, bleomycin, dactinomycin, daunorubicin, doxorubicin, epirubicin, idarubicin, mitomycin, plicamycin

e) complexes of sub-group elements (e.g. Ti, Zr, V, Nb, Ta, Mo, W, Ru, Pt), such as carboplatin, cisplatin and metallocene compounds, such as titanocene dichloride

f) amsacrine, dacarbazine, estramustine, etoposide, hydroxycarbamide, mitoxantrone, procarbazine, temiposide

g) alkylamidophospholipids (described in J.M. Zeidler, F. Emling, W. Zimmermann and H.J. Roth, Archiv der Pharmazie, 324 (1991), 687)

h) ether lipids, such as hexadecylphosphocholine, ilmofosine and analogues, described in R. Zeisig, D. Arndt and H. Brachwitz, Pharmazie 45 (1990), 809-818.

There may be mentioned in particular: cyclosporins, such as cyclosporin A, and cyclosporin derivatives, as well as paclitaxel.

The formulation according to the invention can comprise customary polymers as the polymer, such as, for example, polyacrylates or polymethacrylates (Eudragit E, L, F), celluloses and cellulose derivatives (methylhydroxy-propylcellulose, ethylcellulose, hydroxy-propylcellulose acetate succinate (Aquoat®) or naturally occurring polymers (shellac, waxes, beeswax, polish waxes). The release property of the formulation or of the larger matrix units prepared therefrom can be controlled by the choice of the polymer. A release of the active substance which is delayed only slightly in comparison with non-retarded tablets can thus be achieved by using methylhydroxy-propylcellulose. The use of Eudragit E as the polymer already leads to a delayed release of the active substance in the stomach. If the formulation comprises Eudragit L or F as the polymer, a controlled release of the active substance initially in the intestinal region is possible.

The formulation according to the invention can comprise customary lipids as the lipid, such as, for example, naturally occurring, semi-synthetic and synthetic

triglycerides or mixtures thereof, mono- and diglycerides by themselves or as a mixture with one another or with e.g. triglycerides, naturally occurring and synthetic waxes, fatty alcohols, including their esters and ethers, and lipid peptides. Synthetic mono-, di- and triglycerides, as individual substances or in a mixture (e.g. hydrogenated fat), glycerol tri-fatty acid esters (e.g. glycerol trilaurate, - myristate, -palmitate, - stearate and -behenate) and waxes, such as e.g. cetyl palmitate and cera alba (bleached wax, German Pharmacopeia, 9th edition) and beeswax (e.g. Apifil, Apifac) are particularly suitable.

Further lipids, in some cases with additionally emulsifying (SE = self-emulsifying) properties are glycerol behenate (e.g. Compritol 888 ATO), glycerol tribehenate (Compritol 888), palmitostearate, such as e.g. glycerol palmitostearate (e.g. Biogapress Vegetal ATO BM 297, Precirol Ato 5, Geleol), diethylene glycol, propylene glycol, ethylene glycol, polyglycol and propylene glycol palmitostearate, stearates, such as glycerol stearate (e.g. Precirol WL 2155 Ato) and polyglycol stearate, isostearates, polyalcohol fatty acid esters (e.g. Compritol WL 3284), PEG behenate (e.g. Compritol HD5 ATO), cetyl palmitate (e.g. Precifac Ato), sucrose esters, such as sucrose monodistearate and monopalmitate (e.g. Sucro-Ester W.E. 15), sucrose distearate (e.g. Sucro-Ester W.E. 7), polyglycerol esters, such as polyglycerol isostearostearate (Lafil WL 3254) and palmitostearate, polyglycolized glycerides (e.g. Gelucire, Labrafil, Suppocire), self-emulsifying polyglycol stearate (e.g. Superpolystate), self-emulsifying polyglycol palmitostearate (e.g. Tefose series), glycerides of C_{12}-C_{18} fatty acids (e.g. Lipocire) and mixtures thereof of two or more lipids.

The release property of the formulation or of the larger matrix unit prepared therefrom can be controlled by the choice of the lipid. The release can thus be accelerated by using lipids which are fast degraded in the intestine, since in addition to the release on the basis of diffusion from the matrix, release on the basis of matrix erosion also takes place. The release is more delayed with lipids which are degraded more slowly or lipids which cannot be degraded in the gastrointestinal tract. Dynasan 114 is described as a lipid which can be degraded relatively rapidly by pancreatic lipase/colipase, and the degradation of Dynasan 118 takes place more slowly (C. Olbrich, R.H. Müller, Proceed. Int. Symp. Controlled Rel. Bioact. Mater., Stockholm, 921-922, 1997).

The following groups of substances can be used in particular as excipients:

Fillers from the area of sugars, such as, for example, disaccharides (lactose, sucrose), monosaccharides (glucose, fructose) or polysaccharides (starches, maize or potato starch, cellulose, naturally occurring cellulose powder, microcrystalline cellulose), sugar alcohols, such as, for example, sorbitol or mannitol, or calcium phosphates.

Binders, such as polyvinylpyrrolidone (PVP, Kollidon CL), gelatine, starch glue, celluloses, cellulose ethers or sugars.

According to the invention, it has been found that a formulation in the form of a polymer-containing/lipid-containing compound which has an excipient phase with at least one excipient and/or an active substance phase with at least one active substance and a polymeric phase/lipid phase with at least one polymer/lipid, the polymer

phase/lipid phase of the formulation being incoherent and the excipient and/or active substance phase being coherent, is obtained when the various phases of the formulation are suspended or suspended and dissolved together in a liquid, the polymer phase/liquid phase being insoluble in the liquid, and this suspension is then spray dried.

A formulation in which the polymer phase/lipid phase is free from the excipient and/or active substance phase is obtained in particular by this procedure.

It is also possible to dry the suspension in a moving bed or fluidized bed drier. In this procedure, the phases of the formulation are again suspended or suspended and dissolved together in a liquid, the polymer phase/lipid phase being insoluble in the liquid, and this suspension is then dried in a moving bed or fluidized bed drier.

For carrying out the process according to the invention, the corresponding amounts of polymer/lipid and excipient and/or active substance are suspended or suspended and dissolved in a liquid with the aid of a high-speed stirrer or a disperser, the polymer/lipid being insoluble in the liquid but being present as solid particles, in contrast to the known process with polymer processing. Depending on the polymer/lipid to be suspended, it should be ensured that shearing forces and temperatures which are too high and lead to aggregation or merging of polymer particles/lipid particles do not arise during the dispersing.

The liquid used is, in particular, demineralized water or an aqueous or organic dispersing or suspending agent.

The particular desired viscosity of the suspension to be sprayed in the spray drier, moving bed drier or fluidized

bed drier is controlled via the percentage solids content. In the case of water-soluble excipients, additional possibilities of regulation exist via the concentration and chemical nature thereof (e.g. lactose, excipients with a pronounced viscosity-increasing effect).

A further advantageous embodiment is the addition of wetting agents and/or binders and/or plasticizers (e.g. triethyl citrate, propylene glycol and the like) to the suspension. Particularly suitable binders are polyvinylpyrrolidone, gelatine, starch glue, cellulose, cellulose ethers or sugars. They increase the mechanical resistance of the formulation. The plasticizer allows an influence, which can be validated, on the plasticity, deformability and film-forming properties of the polymer/lipid and therefore allows the release of the active substance to be controlled, in addition to the delayed action effect of the polymer/lipid per se. Plasticizers which can be employed are, above all, triethyl citrate and propylene glycol. However, other internal and external plasticizers which are known as customary additives to polymers/lipids are suitable for controlling the release of the active substance.

The suspension is subsequently spray dried under spray pressures of usually above 20 bar with the aid of suitable one- and multicomponent nozzles in a spraying tower at suitable outlet air temperatures, depending on the sensitivity of the active substances and excipients and on the apparatus design of the spraying tower and its periphery, or is dried in a moving bed or fluidized bed drier.

If necessary, the resulting formulation can then also undergo secondary drying. Secondary drying and/or an additional agglomeration of the formulation on moving bed or fluidized bed driers is possible here.

On the basis of the drying operation in the spray drier or moving bed or fluidized bed drier, the resulting formulation has an approximately spherical form.

It has been recognized according to the invention that the formulation described, which comprises an incoherent polymer phase/lipid phase and a coherent excipient and/or active substance phase, is suitable for use in the preparation of relatively large matrix units with controlled release properties. All the known process can be used for this, so that larger matrix units of any desired shape are obtained, such as, for example, tablets, pellets or cylindrical rods. The known processes for the preparation of extruded or spheronized pellets or for introducing the formulation into capsules can also be carried out with the formulation according to the invention.

It has furthermore been recognized that the formulation according to the invention is particularly suitable for the preparation of larger matrix units and/or tablets with controlled release properties by means of direct compression. This is possible, in spite of the high polymer content/lipid content of the formulation, since, inter alia, a very good flow property and improved compression properties of the formulation are achieved by the process according to the invention.

The preparation of tablets by means of direct compression from a formulation which is free from active substance and is mixed with at least one active substance and, if required, with further excipients, and from a formulation which comprises active substance and, under certain circumstances, can additionally also be mixed with at least one active substance and, if necessary, with further excipients is particularly advantageous.

Coated tablets cores, film-coated or jacketed tablets cores or cylindrical rods in particular are also obtainable, in addition to the customary tablets, by direct tablet-making or direct compression.

The formulation according to the invention can furthermore be used for the preparation of larger matrix units which comprise various active substances or the same active substance in different doses (e.g. layered tablets), each active substance or each dose having its own point in time of release which is independent of the other active substances or doses. For this, a formulation according to the invention comprising active substance, which can also additionally comprise at least one excipient, is mixed with at least one further or the same active substance, if necessary with the addition of auxiliaries, such as, for example, fillers, mould release agents or binders. The mixture is then processed to larger matrix units by means of direct compression or by other known processes. This is particularly advantageous in the case of incompatible active substances, since this procedure leads to a spatial separation of the active substances in the medicament form.

By using the formulation according to the invention in a process for the preparation of larger matrix units, modifications of the release profile are rendered possible, since the active substance or substances in the larger matrix unit are enclosed to different degrees, as a function of the amount of polymer/amount of lipid, and are thus released at different speeds.

The use according to the invention of the formulation for direct compression has the advantage, in particular, that the active substances and/or excipients are exposed to moisture for only a very short time due to the drying

operation used, compared with the conventional wet granulation, which has previously been necessary as a precursor to the compression of polymer-containing formulations. In the drying processes mentioned, the exposure to heat can be controlled and can even be eliminated if drying is carried out in a stream of air at room temperature.

The preparation of pellets may be mentioned as an example of the preparation of larger matrix units by known processes. For this, the formulation according to the invention is extruded with an extruder customary for the preparation of pellets, with the addition of adequate excipients, and is converted into beads of pellet size via a subsequent spheronization. Alternatively, the preparation can be carried out via a perforated roll compactor connected to a pelleting container. Possible apparatuses are a Spheronizer® and Marumizer®. These pellets can also be prepared from the formulation described using a pelleting dish.

These pellets, like the formulation itself, can be introduced, for example, into capsules or pressed to larger units.

The invention is explained in more detail below with the aid of embodiment examples and figures. All the percentage data relate to the weight.

Examples

1. Preparation of a lactose-ethylcellulose formulation (50:50):

The two components are dispersed in demineralized water with the aid of a stirrer. The dispersion is sprayed at a solids content of up to 40 per cent and a spray pump pressure of 30-50 bar in a laboratory spraying tower at

outlet air temperatures of between 70 and 100 degrees Celsius.

The result is a readily free-flowing sprayed agglomerate comprising lactose and ethylcellulose in a particle size distribution of between 1 and 630 µm, the main content of 50-80 % being between 63 and 400 µm.

The formulation prepared in this way is distinguished in particular as being very readily miscible and loadable with active substance on the basis of its feature that the polymeric phase is incoherent and the excipient and/or active substance phase is coherent, and its approximately spherical form and the nature of its surface (cavities, hollows).

In the case of lipophilic active substances, the duration of release of the active substances can be prolonged by a factor of up to three compared with non-retarded tablets by direct mixing with the formulation. The duration of the release can in turn be varied by changing the polymer content in the tablet-making composition, e.g. by admixing a filler of the starch and lactose type.

2. <u>Preparation of a lactose-ethylcellulose formulation comprising acetylsalicylic acid (ASA)</u>:

The preparation is carried out as described in 1., and the components lactose:ethylcellulose:ASA are mixed in a weight ratio of 45:45:10.

3. Preparation of a tablet from a formulation comprising acetylsalicylic acid (ASA):

The lactose-ethylcellulose formulation prepared under 1., which is free from active substance, is mixed with ASA in ratio of 90:10, 0.5 % Aerosil and 1 % magnesium stearate are added to the mixture and the mixture is subjected to direct compression.

4. Preparation of a tablet from a formulation comprising acetylsalicylic acid (ASA):

0.5 % Aerosil and 1 % magnesium stearate are added to the ASA-loaded lactose-ethylcellulose formulation prepared under 2. and the mixture is subjected to direct compression.

5. Preparation of a paracetamol-lactose-ethylcellulose formulation (20:40:40):

All the components are dispersed in demineralized water and the dispersion is adjusted to a desired viscosity, depending on the pumping and pressure. Spraying is carried out by the processes described above. On the basis of their powder properties, the formulation prepared in this way is suitable directly for direct compression, it being possible for the release of the active substance to be delayed to the desired extent by the variably adjustable percentage content of polymer - by admixing further excipients, variable tablet hardness.

6. Preparation of a Compritol-trehalose compound:

Compritol 888 ATO (glycerol tribehenate) was melted, poured into hot water, after addition of 1.2 % Poloxamer 188, and dispersed therein by means of a high-speed Ultra-

Turrax. After cooling, trehalose was dissolved in the aqueous lipid particle dispersion, so that 10 % lipid and 3 % trehalose resulted as the final concentration. This mixture was spray dried in a Mini-Büchi (inlet temperature : 110°C, outlet temperature: 50°C; spray flow: 600 normal litres). A free-flowing lipid-excipient compound was obtained.

7. Preparation of a tablet from a compound with 1 % paracetamol:

9 parts of the lipid-trehalose compound described in example 6 were subjected to direct compression on a Korsch eccentric press with the addition of 0.1 part paracetamol and with admixing of 0.5 % Aerosil 200 and 0.5 % magnesium stearate. Tablet nominal weight 505 mg.

8. Preparation of a tablet from a compound with 10 % paracetamol:

13 parts of the lipid-trehalose compound described in example 6 were mixed with 3 parts of trehalose, 10 % paracetamol was added to this mixture and the mixture was subjected to direct compression on a Korsch eccentric press with admixing of 0.5 % Aerosil 200 and 0.5 % magnesium stearate. Tablet nominal weight 505 mg.

9. Release from a tablet from a compound with 10 % paracetamol:

The release of paracetamol from the tablet prepared in example 8 was determined with the paddle method in accordance with the United States Pharmacopoeia, release medium: water, temperature 37°C. The resulting release curves are shown in figures 5 and 6.

Brief explanation of the figures:

Figure 1:

Figure 1 shows the preparation of a formulation according to the invention via a compound by the process according to the invention: The matrix-forming agent (e.g. polymer particles/lipid particles) is dispersed in water, the excipient and/or active substance is likewise dissolved or dispersed in the aqueous phase and the suspension is sprayed, the water being removed by drying. A formulation which itself is composed of small polymer particles/lipid particles is formed, the intermediate spaces being filled with the excipient (left) or with excipient and active substance (right). The formulation has an incoherent polymeric/lipid phase and a coherent excipient and/or active substance phase.

Figure 2:

Figure 2 shows an example of the use of the formulation according to the invention for the preparation of larger matrix units. The formulation (e.g. of polymer and lactose or of lipid and Flowlac 100 - spray-dried lactose, Meggle, Germany), which is free from active substance, is mixed with the active substance (in powder form), if necessary tablet compression excipients are added and the mixture is subjected to direct compression, e.g. to a tablet.

Figure 3a:

O/W emulsion process known from the prior art: Here, a drop of an organic solvent with matrix-forming agent (e.g. polymer) dissolved therein is dispersed in an aqueous phase (O/W emulsion), the active substance being dissolved (left) or, in the case of insoluble active substance, dispersed (right) in the organic phase. For further explanation, see the text.

Figure 3b:

W/O emulsion process known from the prior art: Here, a drop of water with matrix-forming agent (e.g. water-soluble polymer) dissolved therein is dispersed in an organic phase (O/W emulsion), the active substance being dissolved (left) or, in the case of insoluble active substance, dispersed (right) in the aqueous phase. For further explanation, see the text.

Figure 4:

Figure 4 shows the process according to the invention for the preparation of the formulation according to the invention. The polymeric phase/lipid phase is not dissolved, but dispersed or suspended in drops of water, which are distributed in a gas phase by spraying. An excipient (e.g. lactose, left) or an excipient and an active substance (right) are also dissolved or dispersed or suspended in the drop of water. After removal of the water, an excipient-polymer/lipid formulation which is free from active substance (left) or an active substance-excipient-polymer/lipid formulation (right) is formed, the polymeric phase/lipid phase being incoherent in both cases.

Figures 5 and 6:

Release of paracetamol from a tablet using the formulation according to the invention (example 4). Plot of the amount released as a function of time (figure 5) and as a function of the square root of the time (figure 6).